Adherence to medication in cardiovascular disease

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I have the following potential conflicts of interest to report:

**Lecture fees:** Astra-Zeneca, Bayer, Boehringer-Ingelheim, Menarini, MSD-Vianex, Novartis, Pfizer, Servier, Galenica

**Advisory Boards:** MSD-Vianex, Novartis, Servier.
Adherence to medication in CVD: Agenda

- Definitions
- Adherence measure
- Reasons for non adherence
- Characteristics of treatment adherence
- Predictors of poor adherence
- Consequences of poor adherence
- Strategies to improve adherence
Importance of adherence to medication

“Drugs don’t work in patients who don’t take them”
- Charles Everett Koop, MD

Charles Everett Koop, MD
(October 14, 1916 – February 25, 2013)

- A famous American pediatric surgeon and public health administrator under President Ronald Reagan from 1982 to 1989.
- Koop was known for his work to prevent tobacco use, AIDS, and abortion, and for his support of the rights of disabled children.
Importance of adherence to medication

“Adherence is the key mediator between medical practice and patient outcomes”

Kravitz RL, Melnikow J. Medical adherence research: time for a change in direction. Med Care. 2004; 42; 197-199.
Definitions
The WHO defines **adherence** as “the extent to which the persons’ behavior (including medication-taking) corresponds with agreed recommendations from a healthcare provider”.

With regards to medical treatment it includes:

- initiation of the treatment
- implementation of the prescribed regime
- discontinuation of the pharmacotherapy

*E. Sabat´e, Adherence to Long-Term Therapies: Evidence for Action, World Health Organization, Geneva, Switzerland, 2003*
Compliance: Definitions

- The similar term **therapeutic compliance** is defined as “the extent to which a patient **follows** medical instructions”.


- Drug compliance implies that **the patient follows the doctor's orders** (i.e. the treatment plan is not based on an alliance or contract established between the patient and the physician).”

  Kravitz RL. Med Care. 2004;42;197-199
• Today, the term ‘compliance’ is used less frequently because it implies that only the patients is responsible for the medical treatment.

• The term ‘adherence’ has now replaced ‘compliance’, because it reflects a less paternalistic physician-patient relationship, and includes the responsibility of the caregivers.

Adherence measure
Adherence is difficult to measure

**Methods:**

**Indirect:**
- Asking the patient, **self report** and patient questionnaires.
- Proportion of **days covered** (insurances).
- **Pill count**.
- **Morisky Scale** of medication adherence.

**Direct:**
- Direct visualisation of medication intake.
- Detection of drug or its metabolite concentration in blood or urine (clinical trials).

### Morisky 8-Item Medication Adherence Questionnaire

<table>
<thead>
<tr>
<th>Question</th>
<th>Patient Answer (Yes/No)</th>
<th>Score Y=1; N=0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you sometimes forget to take your medicine?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>People sometimes miss taking their medicines for reasons other than forgetting. Thinking over the past 2 weeks, were there any days when you did not take your medicine?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you ever cut back or stopped taking your medicine without telling your doctor because you felt worse when you took it?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>When you travel or leave home, do you sometimes forget to bring along your medicine?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did you take all your medicines yesterday?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>When you feel like your symptoms are under control, do you sometimes stop taking your medicine?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taking medicine every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?</td>
<td>A = 0; B-E = 1</td>
<td></td>
</tr>
<tr>
<td>How often do you have difficulty remembering to take all your medicine?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>__ A. Never/rarely</td>
<td></td>
<td></td>
</tr>
<tr>
<td>__ B. Once in a while</td>
<td></td>
<td></td>
</tr>
<tr>
<td>__ C. Sometimes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>__ D. Usually</td>
<td></td>
<td></td>
</tr>
<tr>
<td>__ E. All the time</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Scores: 
- 0-2 = low adherence
- 3 or 4 = medium adherence
- 5 or 6 = high adherence

### Measure of adherence

<table>
<thead>
<tr>
<th>Measures</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication Possession Ratio (MPR)</td>
<td>Days’ supply obtained/refill interval or fixed interval</td>
</tr>
<tr>
<td>Dichotomous variable</td>
<td>N/A (arbitrary cutoff value)</td>
</tr>
<tr>
<td>Continuous, Multiple Interval Measure of Medication Gaps (CMG)</td>
<td>Cumulative days without any medication over a series of intervals/total days from the beginning to the end of the time period</td>
</tr>
<tr>
<td>Continuous, Single Interval Measure of Medication Acquisition (CSA)</td>
<td>Days’ supply obtained in each interval/total days in the interval</td>
</tr>
<tr>
<td>Continuous, Single Interval Measure of Medication Gaps (CSG)</td>
<td>Number of days without any medication/total days in the interval</td>
</tr>
<tr>
<td>Pill count</td>
<td>(Number of dosage units dispensed – number of dosage units remained)/(prescribed number of dosage unit per day × number of days between 2 visits)</td>
</tr>
</tbody>
</table>
24% of patients with MI discontinued the therapy 7 days after discharge.

At first month after discharge, 34% of patients discontinued 1 of the 3 medications, and 12% of patients discontinued all 3 medications.

20% of chronic patients do not start the prescribed therapy.

50% of patients quit treatment at 6 months.

Mc Horney

Jackevicius CA. JAMA 2002;288:462-7
Adherence to antihypertensive therapy at 1-year

Corrao, J Hypertens 2008
Non-adherence to heart failure therapy at 1-year

% of Patients

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Όνομα</td>
<td>45</td>
</tr>
<tr>
<td>Δοσολογία</td>
<td>50</td>
</tr>
<tr>
<td>Χρόνος</td>
<td>64</td>
</tr>
<tr>
<td>Απόρριψη</td>
<td>27</td>
</tr>
</tbody>
</table>

Eur J Heart Fail 1999;1:145-9
Adherence to target β-blocker dose and outcome

Acute Decompensated HF post discharge

Cumulative survival

Days post discharge

>75% TD
25-75% TD
<25% TD

P-logrank <0.0001
Reasons for non adherence
ADHERENCE TO LONG TERM THERAPIES: EVIDENCE FOR ACTION. WHO 2003

Reasons for non adherence

The Five Dimensions of Non-Adherence

Social/Economic
- Age & Race
- Socio-economic status
- Illiteracy
- Cost of medications

Patient-related
- Forgetfulness
- Cognitive impairment
- Misunderstood instructions

Therapy-related
- Polypharmacy
- Complexity
- Duration
- Side-effects

Condition-related
- Comorbidities (depression)
- Asymptomatic
- Chronic disease

Health Care System
- Patient-provider relationship
- Overworked HCP
- Lack of incentives

Diapo de JM Castellano. WHO 2003
Characteristics of treatment adherence

- Decreases with time and complexity of pharmacotherapy.
- Is related to lower medication cost.
- Is independently associated with improved outcome.
- Is enhanced with combination therapy.
Adherence to drug treatment represents a surrogate marker for overall healthy behaviour.

People who adhere to healthy lifestyles also tend to take better care of themselves by greater adherence to prescribed treatments.

In a recent study, good statin adherence was associated with a lower probability of having motor vehicle accidents or workplace accidents as well as suffering from diseases unrelated to statin use.

The lower probability of having accidents was related to a more health-conscious lifestyle, such as using screening services.

These observations show that poor adherence identifies individuals at increased risk.

The challenge is to find a comprehensive approach to enhance the factors underlying the ‘healthy adherer’ phenomenon.

Predictors of poor adherence
Predictors of poor adherence to medication

- Advanced age
- Marital status: single
- Low education level
- Non-white race
- Female gender
- Comorbidity burden
- Polypharmacy
- High co-payment

*European Heart Journal. 2011;32:264-268*
The prevalence of comorbid illnesses in clinical trials may differ from those of “real-world” patients.

In recent HF registries more than 67% of patients have ≥2 non-cardiac comorbidities.

More than 25% of patients with HF have ≥6 concomitant diseases.

Whereas in most large clinical trials HF patients had <3 significant comorbid conditions.

Issues with comorbidity

- Increase morbidity and mortality
- Need for polypharmacy
  - Drug adverse reactions
  - Non-adherence to medication
Charlson comorbidity score and 1-year mortality

- Score 0: 12%
- Score 1-2: 26%
- Score 3-4: 52%
- Score 5 or more: 85%

Number of comorbidities or medications and adherence in ACS patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
<th>Mean score (SD)</th>
<th>F-statistic (df)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age groups</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;44 (years)</td>
<td>18</td>
<td>7.1 (0.8)</td>
<td>3.809 (4; 189)</td>
<td>0.005</td>
</tr>
<tr>
<td>45–54 (years)</td>
<td>54</td>
<td>6.8 (1.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>55–64 (years)</td>
<td>65</td>
<td>6.2 (1.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65–74 (years)</td>
<td>29</td>
<td>6.1 (1.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75–84 (years)</td>
<td>24</td>
<td>5.9 (1.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.055</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.399b</td>
</tr>
<tr>
<td>Malay</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indian</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Employment status</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.032</td>
</tr>
<tr>
<td>Employed</td>
<td>99</td>
<td>6.57 (1.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>91</td>
<td>6.13 (1.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ACS subtypes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UA</td>
<td>111</td>
<td>6.29 (1.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSTEMI</td>
<td>40</td>
<td>6.03 (1.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI</td>
<td>39</td>
<td>6.87 (1.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Comorbid conditions</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;3 comorbidities</td>
<td>63</td>
<td>7.15 (1.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3 comorbidities</td>
<td>127</td>
<td>5.97 (1.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Concomitant drugs used</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>&lt;5 medications</td>
<td>23</td>
<td>7.18 (1.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥5 medications</td>
<td>167</td>
<td>6.25 (1.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

≥3 comorbidities and ≥5 medications decrease adherence
Number of medications and adverse drug reactions

Nolan and O’Malley. JAGS 1988; 36: 142-9
Number of medications and compliance

Darnell JC et. al. JAGS 1986; 34: 1-4
**Objective**: Review of 76 studies to assess the association between adherence and the variety of therapeutic classes (electronic monitoring) between 1986-2000.

**Variables**:
- Dose-taking (taking the prescribed number of pills each day).
- Dose-timing (taking pills within the prescribed time frame).

**Results:**

**Nº of Doses**
Adherence was significantly higher:
- For once daily dosing:
  - Versus thrice daily dosing ($p = 0.008$)
  - Versus four times daily dosing ($p < 0.001$)
- And twice daily dosing against for times ($p = 0.001$)

**Dose frequency**
Simpler, less frequent dosing regimens resulted in better compliance across a variety of therapeutic classes.

Influence of copayment on treatment adherence

**Objectives**: To compare statin non-adherence and discontinuation rates of primary and secondary prevention populations.

**Design**: Retrospective cohort utilizing pharmacy claims and administrative databases.

**Definition of lack of adherence**: CMG (%): number of days without therapy over the number of days the patient was actively taking medication. **Non-adherent behaviour CMG > 10%**.

**Population**: 4,802 patients, 2,258 (47%) in secondary prevention and 2,544 patients (53%) in primary prevention.

- Greater grade of copayment, greater possibilities of discontinuation.

- Patients with higher copayment had 4 times higher chance to discontinue the treatment than those with lower copayment.

**Objective:** To assess the availability and affordability of medicines used to treat cardiovascular disease in six low- and middle-income countries.

**Method:** Price of 32 medications, availability, affordability (measured in number of days’ salary to purchase one month of treatment)

- **Number of days’ salary to purchase one month of treatment:**
  - Bangladesh: 1.6
  - Brasil: 5.1
  - Malawi: 18.4
  - Nepal: 6.1
  - Pakistan: 5.4
  - Sri Lanka: 1.5

* Daily doses: ASA 100mg, Atenolol 100mg, ACEI 10mg, Lipid-lowering 20 mg

The medication affordability for CV prevention is low in public health systems. Patients should acquire them in private sector or discontinue the treatment if they can't afford the expenses.
Adherence and outcomes
Objectives: To compare statin non-adherence and discontinuation rates of primary and secondary prevention populations.

Design: Retrospective cohort utilizing pharmacy claims and administrative databases.

Definition of lack of adherence: CMG (%): number of days without therapy over the number of days the patient was actively taking medication.

Non-adherent behaviour CMG>10%.

Population: 4,802 patients, 2,258 (47%) in secondary prevention and 2,544 patients (53%) in primary prevention.

Mean time until discontinuation was 3.7 years in secondary prevention versus 3.4 years in primary prevention.
Adherence in primary vs. secondary prevention

Meta-analysis of 376,162 patients from 20 studies (11 primary CV prevention; 9 secondary CV prevention).

Adherence to prescribed medication is significantly higher in patients in secondary prevention (66%) than in primary prevention (50%) (p=0.012)

Non-adherence is associated with more CV events

Secondary prevention after AMI

MITRA Study
N = 6067

French Study
N = 2320

Sleight. Eur Heart J. 2006;27:1651-1656
Danchin. Am Heart J. 2005;150:1147-1153
Non-adherence to secondary prevention medication is associated with increased CV mortality

**Design:** multicentre prospective cohort of 1521 patients with MI (from PREMIER registry).

**Variables:**
- Use of aspirin, beta-blocker and statin at 1 month after MI.
- Patients discharged with all 3 medications.
- Mortality at 12 months.

At 1 month, 33.7% of patients discontinued use all or part of the treatment.

1-year survival was significantly lower in those patients who **discontinued treatment** 1 month after the AMI (88.5% vs. 97.7%; log-rank \( P < 0.001 \)) compared with those who continued taking all 3 medications.

Patients who **discontinued use of all medications** remained at significantly increased risk of death during follow-up (hazards ratio, 3.81; IC 95%, 1.88-7.72). (multivariable analysis)

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Objective: to determine the extent to which adherence influences the relative risk and all-cause mortality.

Design: meta-analysis of prospective epidemiological studies. High risk population with any CVD.

Results: 44 prospective studies comprising 1,978,919 non-overlapping participants, with 135,627 CVD events and 94,126 cases of all-cause mortality.

Adherence definition: Good adherence: ≥80% taking medication.

Only 60% (95% CI: 52–68%) of the included patients were good adherents.
## RRR of CV events in patients with good adherence

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>No. of CVD events</th>
<th>RRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Adherence to statins</td>
<td>17</td>
<td>1,055,920</td>
<td>96,216</td>
<td>0.85 (0.81, 0.89)</td>
</tr>
<tr>
<td>(2) Adherence to antihypertensive agents</td>
<td>13*</td>
<td>552,143</td>
<td>36,186</td>
<td>0.81 (0.76, 0.86)</td>
</tr>
<tr>
<td>ACE inhibitors/Angiotensin receptor blockers</td>
<td>4</td>
<td>68,781</td>
<td>4,643</td>
<td>0.75 (0.55, 1.01)</td>
</tr>
<tr>
<td>Bela-blockers</td>
<td>4</td>
<td>90,402</td>
<td>10,774</td>
<td>0.83 (0.71, 0.98)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>1</td>
<td>9,168</td>
<td>2,249</td>
<td>0.91 (0.82, 1.01)</td>
</tr>
<tr>
<td>Multiple agents</td>
<td>7</td>
<td>443,264</td>
<td>22,714</td>
<td>0.80 (0.73, 0.89)</td>
</tr>
<tr>
<td>(3) Adherence to aspirin</td>
<td>3</td>
<td>15,253</td>
<td>2,274</td>
<td>0.60 (0.31, 1.16)</td>
</tr>
<tr>
<td>(4) Adherence to any CVD medication</td>
<td>33*</td>
<td>1,615,126</td>
<td>135,627</td>
<td>0.80 (0.77, 0.84)</td>
</tr>
</tbody>
</table>

**Relative Risk Reduction (RRR) of CV events in patients with good adherence is of a 20% (RR 0.80 (0.77-0.84))**

*For individual studies reporting data for more than one medication class the results for the different categories within that study were meta-analysed (fixed effect) before use in the composite calculation.*
### RRR of all-cause mortality in patients with good adherence

<table>
<thead>
<tr>
<th>Medication Category</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>No. of deaths</th>
<th>Proportion (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence to statins</td>
<td>11</td>
<td>291,864</td>
<td>29,605**</td>
<td>0.55 (0.46, 0.67)</td>
</tr>
<tr>
<td>Adherence to antihypertensive agents</td>
<td>11*</td>
<td>205,598</td>
<td>12,288**</td>
<td>0.71 (0.64, 0.78)</td>
</tr>
<tr>
<td>ACE inhibitors/Angiotensin receptor blockers</td>
<td>4</td>
<td>62,196</td>
<td>886**</td>
<td>0.74 (0.69, 0.80)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>7</td>
<td>67,991</td>
<td>5,441**</td>
<td>0.83 (0.69, 1.00)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>1</td>
<td>9,168</td>
<td>2,696</td>
<td>0.97 (0.87, 1.09)</td>
</tr>
<tr>
<td>Multiple agents</td>
<td>3</td>
<td>81,342</td>
<td>2,978</td>
<td>0.49 (0.23, 1.05)</td>
</tr>
<tr>
<td>Adherence to aspirin</td>
<td>3</td>
<td>12,980</td>
<td>1,573</td>
<td>0.45 (0.16, 1.29)</td>
</tr>
<tr>
<td>Adherence to any CVD medication</td>
<td>23*</td>
<td>533,381</td>
<td>94,126**</td>
<td>0.62 (0.57, 0.67)</td>
</tr>
</tbody>
</table>

**Relative Risk Reduction of all-cause mortality in patients with good adherence is of a 38% (RR 0.62 (0.57-0.67))**

*For individual studies reporting data for more than one medication class the results for the different categories within that study were meta-analyzed (fixed effect) before use in the composite calculation.

**Groups in which not all studies reported the number of deaths.

Globally (assuming poor adherence of a 40%) 9.1% of all events that occur are due to poor adherence in patients with prescribed cardiovascular medications.

Chowdhury et al. Eur Heart J 2013
### Studies relating non-adherence to treatment with increased CV morbi/mortality

<table>
<thead>
<tr>
<th>Autor</th>
<th>Design (country)</th>
<th>No. patient (age range)</th>
<th>Patient condition</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mukherjee et al., 2004</td>
<td>Registry (USA)</td>
<td>1,264 (63.7 ± 13.3)</td>
<td>ACS</td>
<td>Significant improvement (p&lt;0.001) at 6-month follow-up for the combination therapy with 4 drugs: an antiplatelet agent, statin, ACE inhibitor and β-blocker. Improved survival curve with 4&gt;3&gt;2&gt;1 drugs.</td>
</tr>
<tr>
<td>Danchin et al., 2005</td>
<td>Registry (France)</td>
<td>2,119 (58-79)a (51-72)b</td>
<td>Post-AMI</td>
<td>One-year survival was 97% in those discharged with triple combination therapy with antiplatelet agents, β-blockers and statins vs. 88% in those who received none, 1 or 2 of these medications (p&lt;0.0001).</td>
</tr>
<tr>
<td>Aros et al., 2006</td>
<td>Registry (Spain)</td>
<td>5,397 (65.4 ± 12.8)</td>
<td>Post-AMI</td>
<td>The combined prescription of β-blockers and ACE inhibitors had an additive effect on the one-year survival rate in post-MI patients.</td>
</tr>
<tr>
<td>Dagenais et al., 2006</td>
<td>HOPE and EUROPA Subgroup (USA, Canada, Europe, South America)</td>
<td>29,805 HOPE (66 ± 7) EUROPE &gt; 18</td>
<td>—</td>
<td>Clear benefit of lipid-modifying drugs + β-blockers + antiplatelet agents.</td>
</tr>
</tbody>
</table>
Studies relating non-adherence to treatment with increased CV morbi/mortality

<table>
<thead>
<tr>
<th>Autor</th>
<th>Design (country)</th>
<th>No. patient (age range)</th>
<th>Patient condition</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleigh, 2006</td>
<td>Registry (USA, America, Europe, Australia, Japan)</td>
<td>6,067 &gt; 55</td>
<td>Post-MI</td>
<td>Post-MI survival significantly improved in patients who received four medications (acetylsalicylic acid, β-blocker, ACE inhibitor and statin) compared with those who received none, one or two agents.</td>
</tr>
<tr>
<td>Ho et al., 2006</td>
<td>Registry (USA)</td>
<td>2,498 (63.5 ± 13.7)c (59.6 ± 12.2)d</td>
<td>Post-MI</td>
<td>Medication discontinued at one month (ASA, β-blockers and statins) correlated with lower one-year survival (88.5% vs. 97.7%; log-rank p&lt;.001) compared with patients who continued taking 1 or more medications.</td>
</tr>
<tr>
<td>Zeymer et al., 2011</td>
<td>Registry (Germany)</td>
<td>19,998 (55-78)</td>
<td>Post-AMI</td>
<td>Combination of β-blockers + acetylsalicylic acid + ACE inhibitors + statins reduced one-year mortality in post-AMI patients.</td>
</tr>
<tr>
<td>Rasmussen et al., 2007</td>
<td>Observational study (Canada)</td>
<td>31,455 (&gt; 66)</td>
<td>Post-AMI</td>
<td>Survival correlated with Adherence to the combined use of statins and β-blockers.</td>
</tr>
<tr>
<td>Autor</td>
<td>Design (country)</td>
<td>No. patient (age range)</td>
<td>Patient condition</td>
<td>Conclusion</td>
</tr>
<tr>
<td>-----------------------</td>
<td>--------------------------</td>
<td>-------------------------</td>
<td>-------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Jackevicius et al., 2008</td>
<td>Retrospective cohort study (Canada)</td>
<td>4,591 (&gt; 65) (76.33 ± 7.23)</td>
<td>Post-MI</td>
<td>Primary non-adherence to ACE inhibitors, antiplatelet agents, β-blockers and calcium channel blockers was associated with an increased risk of death at one year after AMI.</td>
</tr>
<tr>
<td>Chowdry et al. 2013</td>
<td>ESC Meta-analysis Europe</td>
<td>1,978,019</td>
<td>Patients with high CV risk</td>
<td>Adherent patients presented a 20% decrease in the relative risk of suffering a CV event and a 35% decrease in the relative risk of death from any cause in comparison with non-adherent or partially-adherent patients. More than 9% of cardiovascular events can be attributed to non-Adherence.</td>
</tr>
<tr>
<td>Kumbhani et al. 2013</td>
<td>Prospective Registry</td>
<td>37,154</td>
<td>Patients with high CV risk</td>
<td>The risk of suffering CV events was highest in non-Adherent patients and in those who, although initially adherent, abandoned the medication over the study’s 4-year follow-up.</td>
</tr>
<tr>
<td>REACH Registry</td>
<td>MI FREE secondary analysis</td>
<td>4,117 54 ± 7.6</td>
<td>Post-AMI</td>
<td>Patients adhering to treatment with statins, beta-blockers and ACE inhibitors/ARBs presented significantly lower incidence of cardiovascular events than non-adherent or partially-adherent patients.</td>
</tr>
<tr>
<td>Bansilal y et al. 2014</td>
<td>Retrospective analysis</td>
<td>4,015</td>
<td>Post-AMI</td>
<td>At 2-years follow-up, the fully-adherent group (adherence &gt;80%) had a lower percentage of cardiovascular events than non-adherent patients (18.9% vs. 26.3%; HR=0.73 CI-0.61-0.86, p&lt;0.0004) and partially-adherent patients (18.9% vs. 24.7%; HR=0.81 CI-0.69-0.96, p&lt;0.016). No differences were observed between the non-adherent and partially-adherent patient cohorts (p=0.22).</td>
</tr>
</tbody>
</table>
Strategies to promote Adherence
- Reduce the number of doses to the lowest feasible level.
- Provide clear advice regarding the benefits and possible adverse effects of the medication, as well as the dose duration, regimen and administration.
- Consider patients' habits and preferences.
- Ask patients in a non-judgemental way how the medication works for them and discuss possible reasons for non-Adherence (e.g. side effects, concerns, etc.).
- **Implement continuous monitoring and feedback.**
- In the case of lack of time, seek the help of an assistant or specialised nurse whenever it is necessary and feasible.
- Consider combined behavioural interventions.

- **Pharmacological strategies**
  
  - Use different formulations of fixed-dose combinations to reduce the daily number of pills and doses.
Effect of fixed antihypertensive combination on adherence

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dezii CM et al, 2000</td>
<td>0.74 (0.65, 0.84)</td>
<td>18.4</td>
</tr>
<tr>
<td>Dezii CM et al, 2000</td>
<td>0.71 (0.62, 0.80)</td>
<td>18.5</td>
</tr>
<tr>
<td>NDC Dataset, 2003</td>
<td>0.81 (0.77, 0.86)</td>
<td>37.8</td>
</tr>
<tr>
<td>Taylor AA et al, 2003</td>
<td>0.74 (0.67, 0.81)</td>
<td>25.2</td>
</tr>
<tr>
<td>Overall</td>
<td>0.76 (0.71, 0.81)</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Heterogeneity chi² = 6.30 (p = 0.10)

Publication Bias (Egger’s) p = 0.05

Bangalore, JACC 2007
Increased Persistence with Fixed-dose Combination Therapy Compared with Free Combination Therapy

Persistence defined as patients remaining on treatment for a duration of 12 months

Lisinopril/HCTZ (n=1,644); lisinopril + diuretic (two pills; n=624)
Statistical significance (p<0.05) seen at Months 6 and 12

Dezii. Manag Care 2000
Highly Compliant Patients are More Likely to Attain BP Goal

Compliance (measured using medication possession ratio)

- High (≥80%) (n=629)
- Medium (50–79%) (n=165)
- Low (<50%) (n=46)

Patients with BP control* (%)

- High (≥80%) 43%
- Medium (50–79%) 34%
- Low (<50%) 33%

Odds ratio = 1.45
p=0.026 (controlling for age, gender and co-morbidities)

*<140/90 mmHg or <130/85 mmHg for patients with diabetes

Better Compliance with Antihypertensive Drugs Leads to a Decreased Risk of Hospitalization

![Bar chart showing the relationship between level of compliance and all-cause hospitalization risk.](chart)

- **All-cause hospitalization risk (%)**
  - 1–19 (n=350): 44%
  - 20–39 (n=344): 39%
  - 40–59 (n=562): 36%
  - 60–79 (n=921): 30%
  - 80–100 (n=5,804): 27%

* *p<0.05 vs 80–100% compliant group

Sokol et al. Med Care 2005;43:521–30
Combination antihypertensive pills lead to higher adherence rate

Meta-analysis of studies with combination pills showing to reduce BP and estimate of reduction of CV events (1).

A combination pill is a cost effective strategy (2).


2. Lea-Laba. MJA 2014
Fixed-dose combinations are associated with a better adherence in all clinical settings

- **Design**: Meta-analysis of studies which involved fixed-dose combination (FDC) versus free-drug components (FC) of the regimen given separately and reported patient’s compliance.

- **Objective**: To demonstrate that with fixed-dose combinations increases adherence.

- **Results**: 9 studies; n=11,925 FDC patients and n=8,317 FC patients.

Fixed-dose combination decreased the risk of medication non-compliance by 26%.

(RR: 0.74; 95% [IC], 0.69-0.80; P = 0.0001).

## Improved Adherence Through Fixed-Dose Combinations for Cardiovascular Prevention

<table>
<thead>
<tr>
<th></th>
<th>Study Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IMPACT Study: BMJ 2014;348:g3318 doi: 10.1136/bmj.g3318. Selak V et al.</td>
</tr>
<tr>
<td>2</td>
<td>KANYINI-GAP Study: Patel et al. Preventive Cardiology</td>
</tr>
<tr>
<td>3</td>
<td>UMPIRE Study: Thom et al. JAMA 2013;310(9):918-929</td>
</tr>
<tr>
<td>4</td>
<td>FOCUS Study: Castellano. JACC 2014</td>
</tr>
</tbody>
</table>
Impact

- Objective: To assess whether fixed-dose combination (FDC) delivery of aspirin, statin, and 2 blood pressure–lowering agents vs. usual care improves long-term adherence.
- Design: Randomized, open-label, blinded-end-point trial.
- Patients: 513 participants with CVD (45%) or at high risk of CVD (Estimated CV risk 5 years >15%). Follow-up 12 months.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Fixed dose combination (n = 256)</th>
<th>Usual care (n = 257)</th>
<th>Treatment effect* (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcomes†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (%) with self reported current use of antiplatelet, statin, and ≥ 2 BP lower drugs at 12 months.</td>
<td>208 (81)</td>
<td>119 (46)</td>
<td>1.75 (1.52 to 2.03)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Selak. BMJ 2014
Kanyini Gap

- **Objective:** To assess whether fixed-dose combination (FDC) delivery of aspirin, statin, and 2 blood pressure–lowering agents vs. usual care improves long-term adherence.
- **Design:** Randomized, open-label, blinded-end-point trial.
- **Patients:** 623 participants with CVD (68%) or at high risk of CVD (Estimated CV risk 5 years >15%). Follow-up 18 months.

![Bar chart showing adherence rates](chart.png)
Objective: To assess whether fixed-dose combination (FDC) delivery of aspirin, statin, and 2 blood pressure-lowering agents vs. usual care improves long-term adherence.

Design: Randomized, open-label, blinded-end-point trial.

Patients with or at high risk of CVD. Follow-up 15 months.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fixed-Dose Combination (n = 1002)</th>
<th>Routine care (n = 1002)</th>
<th>Treatment effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence (%)</td>
<td>86</td>
<td>65</td>
<td>1.33 (1.26 a 1.41)</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>129.2</td>
<td>131.7</td>
<td>-2.6 (-4.0 a -1.1)</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L (mg/dL)</td>
<td>2.18 (84.3)</td>
<td>2.29 (88.5)</td>
<td></td>
</tr>
</tbody>
</table>
### Polypill Concept

#### Cumulative reduction of CV risk by modifying lifestyle habits and taking a polypill

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Potential CVD risk reductions of individual components</th>
<th>Cumulative risk reductions at differing levels of adherence&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>50%</td>
</tr>
<tr>
<td><strong>Lifestyle cumulative risk reduction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking cessation</td>
<td>30%&lt;sup&gt;60&lt;/sup&gt;</td>
<td>15%</td>
</tr>
<tr>
<td>Healthy diet</td>
<td>30%&lt;sup&gt;61&lt;/sup&gt;</td>
<td>15%</td>
</tr>
<tr>
<td>Physical activity</td>
<td>20%&lt;sup&gt;63&lt;/sup&gt;</td>
<td>10%</td>
</tr>
<tr>
<td>Combined lifestyle (smoking + diet + physical activity) modification</td>
<td>50%&lt;sup&gt;62&lt;/sup&gt;</td>
<td>26%</td>
</tr>
<tr>
<td><strong>Polypill cumulative risk reduction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polypill, half standard dose</td>
<td>50%</td>
<td>25%</td>
</tr>
<tr>
<td>Polypill, standard dose</td>
<td>60%</td>
<td>30%</td>
</tr>
<tr>
<td><strong>Lifestyle (shown at 50–90% levels of adherence) + polypill (included at constant 75% adherence in all columns) estimated cumulative risk reduction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polypill (half dose with 75% adherence) + smoking cessation</td>
<td></td>
<td>53%</td>
</tr>
<tr>
<td>Polypill (half dose with 75% adherence) + combined lifestyle modification</td>
<td></td>
<td>63%</td>
</tr>
<tr>
<td>Polypill (full dose with 75% adherence) + smoking cessation</td>
<td></td>
<td>60%</td>
</tr>
<tr>
<td>Polypill (full dose with 75% adherence) + combined lifestyle modification</td>
<td></td>
<td>71%</td>
</tr>
</tbody>
</table>

<sup>a</sup>estimation
Simple interventions save lives!

All-cause mortality for patients receiving polypharmacy according to compliance score at the screening visit

Effect of telephone intervention by a pharmacist on all-cause mortality in patients receiving polypharmacy

RR=2.9
RR=1.8
RR=0.59

Br Med J 2006;333:522
Simple interventions save lives!

Individualized multidose adherence package containing a week’s medication clearly labelled with day and time of administration.

American College of Preventive Medicine

Simplify regimen
Impart knowledge
Modify patient beliefs and human behavior
Provide communication and trust
Leave the bias
Evaluate adherence

Physicians should be aware that adherence to medication reflect generally better health behaviour.

Reducing dosage demands in persons at high CVD risk may result in the prescription of combination pharmacotherapy, the ‘polypill’. Recently, a randomized phase II trial in middle-aged individuals without CVD demonstrated that the ‘Polycap’ formulation could conveniently reduce multiple risk factors.
Thank you

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